OPTIMAL TREATMENT OF ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is typically treated with cholinesterase inhibitors (ChEIs) donepezil, rivastigmine, and galantamine, as well as, the N-methyl D-aspartate receptor antagonist, memantine. ChEIs have been shown to produce statistically significant improvements in Alzheimer’s disease (especially in cognition and global functioning); however, no recommendations are available related to when to start and discontinue therapy in patients with AD. This issue of CLIPS briefly summarizes an article that discusses the optimal initiation, duration, and discontinuation of therapeutic agents for AD.


Introduction
- Alzheimer’s disease (AD) affects one in nine people >65 years and one-third of people aged ≥85 years in the United States.
- The prevalence of AD is expected to triple from 5 million to 13.8 million by 2050.
- There is a lack of therapies that have been shown to reverse or halt AD progression.
- Currently, there are 5 agents that are approved by the FDA for the symptomatic treatment of AD: cholinesterase inhibitors (e.g., tacrine, donepezil, rivastigmine, galantamine) and the N-methyl D-aspartate (NMDA) receptor, memantine.
- As a result of lack of innovation for AD medications, manufacturers are altering the formulations and dosage of current medications.
- Current guidelines provide limited utility in the optimal duration of these agents for AD.

Tacrine
- First cholinesterase inhibitor approved by the FDA.
- One meta-analysis of seven studies revealed no significant benefit with tacrine on cognitive or behavioral measures.
- Increased adverse effects were observed in the meta-analysis included elevated alanine aminotransferase levels and other hepatic abnormalities. These concerns led to its discontinuation in the United States.

Donepezil
- Initial approval was for mild-to-moderate AD. Currently, donepezil is approved for mild to severe AD.
- Doses include 5-10 mg/day for mild to moderate and 10-23 mg/day for moderate to severe AD.
- Significant improvements have been observed with donepezil for cognitive function, activities of daily living, and behavior.
- The additional dosage, 23 mg/day, also is associated with significant improvements in cognition; however, its use is associated with increased treatment-emergent adverse effects (e.g., nausea, vomiting, diarrhea) compared to the 10 mg/day formulation.
- Donepezil should be reserved for patients with moderate-to-severe AD who have been on stable donepezil 10 mg/day for at least 3-6 months, with limited improvement.

Rivastigmine
- Rivastigmine is noted for a longer period of enzyme inhibition and is available as a capsule, oral solution, or transdermal patch.
- The capsule formation is efficacious at doses of 6-12 mg/day. Currently, rivastigmine is the only CHEI that is available as a transdermal patch. Increased adherence, fewer adverse effects, and decreased fluctuations in drug concentrations may be observed with the patch.

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Rivastigmine (continued)
- Patients receiving the patch may experience skin irritation.
- Patients with mild-to-moderate AD may receive 4.6 mg/24 h to 9.5 mg/24 h and the dose may be increased if the patient is not responding to 13.3 mg/24 hour.

Galantamine
- Galantamine is indicated for the treatment of mild-to-moderate AD and is available as a once-daily extended release capsule, twice-daily immediate-release tablet, and an oral solution.
- The dose typically ranges from 16-24 mg/day.

Comparative efficacy
- No significant differences in treatment effect have been observed for the three different ChEIs. The effects of these agents appear to be modest.
- The agents do have a dose response related to clinical efficacy.

Adverse drug reactions
- ChEIs appear to be well tolerated. The most frequent adverse events are nausea, vomiting, diarrhea, dizziness, and weight loss.
- Syncope, bradycardia, permanent pacemaker insertion, and hip fracture have also been observed.
- One study indicated that treatment with ChEIs were associated with a doubling of hospitalization for bradycardia.
- Monitoring in the elderly population receiving ChEIs is recommended.

End of life care
- In a survey of hospice medical directors, most did not feel that ChEIs were efficacious at the end of life; however, they had trouble discontinuing the agents because of the family’s request.
- Clinicians should discuss with the family the role of ChEIs in end-of-life treatment of AD due to the modest benefits, potential adverse effects, and costs.

Combination with memantine
- Approved for use in patients with moderate to severe AD.
- Significant benefits with a combination of memantine 20 mg/day with a CHEI (e.g., donepezil 10 mg/day) has been observed compared to placebo.
- However, controversy still exists regarding whether combination therapy is associated with benefit.
- Current recommendations indicate that patients with moderate-to-severe AD who are naïve to therapy may benefit from combination therapy. One drug must be added before the other to determine tolerability.

Summary
- ChEIs provide modest, significant improvements in patients with AD.
- If patients do not respond to traditional doses, higher doses can be considered with monitoring for adverse effects.
- Therapy should be continued until the terminal phase of AD, unless lack of efficacy or adverse effects occurs.
- Clinicians should discuss benefits and risks in patients with AD receiving ChEIs at the end of life.

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